

REVISED VIEWS OF THE REFRACTORY PERIOD,
IN RELATION TO DRUGS REPUTED TO PROLONG
IT, AND IN RELATION TO CIRCUS MOVEMENT.

BY T. LEWIS AND A. N. DRURY.

[*Reprinted from "Heart."*

Vol. XIII, No. 1, August, 1926.]

WELLCOME INSTITUTE LIBRARY	
Coll.	weIMOmec
Coll.	pam
No.	WG 200
	1 9 26
	L 67 r



22500892200

REVISED VIEWS OF THE REFRACTORY PERIOD, IN RELATION
TO DRUGS REPUTED TO PROLONG IT, AND IN RELATION
TO CIRCUS MOVEMENT.

By T. LEWIS and A. N. DRURY.*

(From the Cardiac Department, University College Hospital Medical School).

IN a series of articles from this laboratory circus movement has been discussed, and the actions of certain drugs, notably those affecting auricular fibrillation and flutter, have been explored. Related observations have been continued and further information has been obtained which places certain of the previous observations in a new light. We propose in the present communication briefly to revise the most important of these questions which are thus reopened. The position as it now exists may be most conveniently shown by a short historical résumé of the more recent observations.

Drury and Andrus² investigated the effects of hydrogen-ion concentration upon the muscle of the dog's auricle perfused with Locke's solution, and were able to bring forward evidence that a condition akin to decrement arises when the perfusate is on the acid side of normality and oxygen free. The condition is one in which an impulse is found to slow down as it travels through muscle, sometimes dying out completely. Drury,¹ who was simultaneously investigating the meaning of intra-auricular block produced by pressure or by cold, found that both these influences led to a similar anomaly of conduction. More important from our present standpoint, he found that the phenomenon in question may seriously interfere with the accurate measurement of absolute refractory periods; failure of muscle to respond to an early testing shock, may be more apparent than real; for, while the muscle may actually respond, the excitation wave so started may die out before reaching a distant point at which the recording electrodes lie. Owing to similarities in the conduction of impulses through muscle compressed and cooled and muscle under the influence of quinidine and strophanthin, the question arose as to whether a similar disappearance of very early excitation waves might not happen in shorter stretches of muscle, and in consequence prolong the estimate of the refractory period of muscle affected by these drugs.

* Working on behalf of the Medical Research Council.

Lewis and Master⁸ in investigating *A-V* conduction observed a number of new phenomena interpretable on similar lines to these. They found, when heart block is present, that over a certain period of the cycle termed by them the "phase of interference" an impulse which fails to be conducted from auricle to ventricle, nevertheless influences the passage of the succeeding impulse, postponing or preventing the ventricular response. The "phase of interference" was found to commence immediately after the period which can be regarded as corresponding to the absolute refractory state of the *A-V* tissues and may be traced as far as the point at which conduction from auricle to ventricle occurs; and the interference was regarded as due to the passage of the corresponding impulse through a limited portion of the conducting tract. Thus, when the impulse falls early, the response or non-response of the *A-V* tissues is gauged, not by response or non-response of the ventricle to that particular impulse, but by the presence or absence of its effect on subsequent conduction. The observations suggested a re-examination of the original curves which served to measure the refractory period of auricular muscle poisoned by quinidine and strophanthin and, when this was done, corresponding phenomena were found. In these experiments the absolute refractory period of the auricle, driven by the rhythmic shocks, was tested by means of break shocks falling with varied prematurity in the cycle; certain of these gave response, certain did not; the dividing line was drawn between these two series and we took it to represent the absolute refractory period; in thus measuring the period we followed custom. Nevertheless, the values obtained in a number of experiments were not those of the absolute refractory period as will be shown presently.

Drury and Love⁴, in an article published with this, have fully examined the effect of veratrin upon the refractory period from the same point of view and find that when the "phase of interference" is allowed for, the absolute refractory period is not prolonged by this alkaloid though, as estimated by simple response or non-response, it seems conspicuously increased. They are able to give accurate measures of the actual and the apparent refractory period in this instance, and to show their considerable divergence. To these Love⁹ adds his more recent observations upon the action of quinidine and strophanthin upon the tortoise ventricle.

The original curves of our old observations upon the effects of quinidine⁶ and strophanthin⁵ on the dog's auricle give accurate measures of the apparent period; in some instances, though by no means in all, they also allow us on re-examination to estimate the actual period. The method of obtaining the last value is fully described in Drury and Love's article. To exemplify, we take a tabulated statement from our previous paper (*NG.*, Table III of that article⁶) and republish it as present Table I. The dividing line in this table (marked R.P.) separates the periods of simple response and non-response, and measures the absolute refractory period as it was apparent to us before and after dosing the animal with quinidine. We have reconstructed this table and now include as responses, both the visible response in the

TABLE I.

(Extracted from Table III., Heart, Vol. IX., page 63).

		Dog N.G. (kilo. 9.75)				
		Before	After (grammes total)			
Auricular rate		202	0-10	0-20	0-20	0-25
			209	207	230	200
R.P.		0-168	0-194			
		0-157	0-165	0-208		
		0-152	0-160	0-195		
		0-143	0-160	0-182	0-224	0-212
		0-141	0-146*	0-179	0-206	0-207
		0-132	0-145	0-173	0-197	0-203
		0-131	0-140	0-162	0-188	0-201
		0-130	0-120	0-157	0-183	0-186
		0-118	0-112	0-120	0-166	0-178
R.P.						
		0-109	0-109	0-092	0-161	0-174
		0-108	0-099	0-084	0-152	0-166
		0-100			0-145	0-166
		0-098				
		0-088				
		0-082				
Coil at	6 cm.	6 cm.	6 cm.	6 cm.	6 cm.	6 cm.
Threshold at	13.5 cm.	—	—	—	—	—

* Italicised values represent apparent non-response.

TABLE II.

(Values corrected and supplemented).

		Dog N.G. (kilo. 9.75)				
		Before	After (grammes total)			
Auricular rate		202	0-10	0-20	0-20	0-25
			209	207	230	200
R.P.			0-194			
			0-165	0-208		
			0-160	0-195		
		0-168	0-160	0-182	0-183	0-212
		0-157	0-146	0-174	0-166	0-207
		0-152	0-145	0-173	0-161	0-203
		0-143	0-143	0-162	0-152	0-201
		0-141	0-140	0-158	0-146	0-186
		0-132	0-132	0-157	0-145	0-174
		0-131	0-123	0-156	0-145	0-166
R.P.						
		0-130	0-130	0-127	0-139	0-143
		0-118	0-112	0-126	0-134	0-131
		0-112	0-109	0-120	0-124	0-129
		0-109	0-099	0-092	0-121	
		0-108		0-084		
		0-100				
		0-098				
		0-088				
		0-082				
Coil at	6 cm.	6 cm.	6 cm.	6 cm.	6 cm.	6 cm.
Threshold at	13.5 cm.	—	—	—	—	—

original curves (as previously) and also the concealed responses which affect the response of the auricle to the succeeding rhythmic shock (Table II). To render this table more complete, we have also added a few new values, obtained from this same series of plates. In Table I the estimated value of the refractory period rises from 0.130 to 0.193 of a second under successive doses of quinidine; in Table II, the rise is much more doubtful. This revised table and the remaining original tables, revised in the same way, show us that the great prolongation of the absolute refractory period of the dog's auricle, displayed by the usual method, is more apparent than real; but do not decide with sufficient accuracy the precise effects of quinidine upon the period. That is so because the observations were not arranged so that the stimulus following our testing shock fell always at a suitable point to display the after-effect of the concealed response.

To settle this point and to determine in a more decisive way the error in measuring the R.P. by the usual method, one of us (A. N. D.) has undertaken two fresh experiments, in which the method which is fully described in the paper of Drury and Love⁴ has been used. The measurements from the two dogs are shown in Table III. In this table the first testing shocks which fail to affect the response to the second testing shock are shown in italicised numerals, those which either delay or abolish this response in ordinary numerals, and those which themselves give rise to a recordable response in

TABLE III.

	<i>Dog ZC.</i> Controlled auricular rate = 176 per minute.			<i>Dog ZF.</i> Controlled auricular rate = 166 per minute.				
	Before	After (grammes total)		Before	After (grammes total)			
		0.05	0.10		0.025	0.050	0.100	
Abs. R.P.		0.159*				0.226	0.232	
		0.152				0.220	0.213	
		0.140					0.206	
		0.134		0.204	0.210	0.198	0.188	
		0.131	0.163	0.200	0.206	0.189	0.173	
		0.127	0.158	0.184	0.195	0.178	0.156	
		0.110	0.144	0.171	0.170	0.167	0.145	
		<i>0.109</i>	0.130	0.154	0.164	0.147	0.136	
	0.127			0.154	0.156	0.134	0.128	
	0.110	0.097	0.116	0.148	0.143	0.128	0.110	
		<i>0.106</i>	<i>0.092</i>	<i>0.109</i>	<i>0.134</i>	<i>0.130</i>	<i>0.115</i>	<i>0.098</i>
		<i>0.105</i>	<i>0.090</i>	<i>0.090</i>	<i>0.117</i>	<i>0.115</i>	<i>0.111</i>	<i>0.083</i>
		<i>0.105</i>			<i>0.111</i>			<i>0.077</i>
Average Abs. R.P. (new method)	0.108	0.094	0.112	0.141	0.137	0.121	0.104	
Average R.P. (usual method)	0.108	0.132	0.151	0.141	0.177	0.199	0.222	

* Heavy type = visible responses.

Ordinary type = concealed responses.

Italicised type = non-response.

block numerals. The measurements support the conclusions already arrived at from our original records that under quinidine the lengthening of the refractory period is more apparent than real, and show in addition, that the real absolute refractory period may be actually shortened by this drug.

The shortening of the period is well displayed in Dog *ZF*, where the refractory period measured by the usual method is conspicuously lengthened.

In view of what has been said, it should be apparent that no measurements of the absolute refractory period of cardiac muscle which have been obtained by the method of simple response or non-response and which have also shown conspicuous lengthening of the period, can be regarded as reliable. All such have become open to revision. There are many such measurements in past writings, but we shall confine ourselves to our own.^{3 5 6} Our previous statements, that quinidine and strophanthin prolong the absolute refractory period of mammalian auricular muscle, are based on evidence which we have now criticised. If these statements are no longer justified by actual evidence, it remains to consider to what extent conclusions based on them still hold. Now these last conclusions apply chiefly to the action of the drugs named upon waves circulating in the auricle^{6 and 7}. From this point of view, although our original measurements under quinidine and strophanthin were not of the absolute refractory period in its proper sense, they measured that which it was most desirable for us to obtain, namely, the *effective refractory period*. Although the end of the absolute refractory period signals the instant at which the muscle will again respond, at least in part, it does not necessarily signal the first instant at which it will again transmit a propagated wave to any distance.

If therefore, the term absolute refractory period, or more briefly refractory period, is read in our previous publications as meaning the *effective refractory period*, the conceptions expressed as to the action of quinidine and strophanthin upon circus movement, require no revision. Thus, it is our conception that circus movement is brought to an end by quinidine by the action of the drug in prolonging the effective refractory period of the muscle.*

One further matter requires comment. In explaining many effects previously recorded, and particularly varieties of intra-auricular block, it has been assumed that the muscle in its recovery passes through what has

* Certain incidental conclusions which have been drawn regarding the recovery of excitability and of conduction under quinidine and strophanthin are affected. Thus, because the threshold value of shocks required to drive the auricle rhythmically was raised but little under quinidine, this was thought to be sufficiently explained by a rise in the absolute refractory period, and by the consequent shortening of the period of rest (see a previous article⁶, page 60). If there is no material lengthening of the absolute refractory period under quinidine, then the rest period is not materially shortened, and the rise in the threshold value would then be attributable to an actual effect of quinidine on the recovery curve.

Similar considerations apply to the statements regarding fibre conduction in a previous article⁵ on strophanthin.

Doubt is also thrown, for the same reason, upon the conclusion drawn by Lewis and Master⁸ that quinidine lengthens the refractory period of the *A-V* node.

been termed a partially refractory state, meaning that some fibres become responsive earlier than others. It is quite probable that intra-auricular block, as it has been observed under strophanthin, is due in large part at all events to a phenomenon akin to decrement. But in this instance and in others of which a state of partial refractoriness has been invoked in explanation, it seems essential, owing to the sinuous paths along which excitation waves are propagated, to conceive of fibres or tracts of fibres as responding or conducting unequally. When individual fibres or tracts of fibres seemingly fail to respond, it is conceivable that the failure may be absolute or that it may be relative in the sense that conduction occurs only for limited distances. The precise meaning of the phenomena underlying what has been termed *partial refractoriness* on the one hand and a *condition akin to decrement* on the other, and their inter-relationships, is still unclear; the further discussion of these matters may be more appropriately deferred until more observational work has been undertaken.

REFERENCES.

- ¹ DRURY. *Heart*, 1925-6, XII, 143.
- ² DRURY AND ANDRUS. *Heart*, 1924, XI, 389.
- ³ DRURY, HORSFALL AND MUNLY. *Heart*, 1921-2, IX, 365.
- ⁴ DRURY AND LOVE. *Heart*, 1926, XIII, 77.
- ⁵ LEWIS, DRURY AND ILIESCU. *Heart*, 1921-2, IX, 21.
- ⁶ LEWIS, DRURY, ILIESCU AND WEDD. *Heart*, 1921-2, IX, 55.
- ⁷ LEWIS, DRURY, WEDD AND ILIESCU. *Heart*, 1921-2, IX, 207.
- ⁸ LEWIS AND MASTER. *Heart*, 1925-6, XII, 209.
- ⁹ LOVE. *Heart*, 1926, XIII, 87.

CONTENTS

	PAGE
IN MEMORIAM	i
ARTHUR ROBERTSON CUSHNY, M.A., LL.D., M.D., F.R.S. (<i>Professor of Materia Medica and Pharmacology, University of Edinburgh.</i>)	
OBSERVATIONS UPON THE REGULATION OF BLOOD-FLOW THROUGH THE CAPILLARIES OF THE HUMAN SKIN	1
By THOMAS LEWIS. (<i>Cardiac Department, University College Hospital Medical School.</i>)	
VASCULAR REACTIONS OF THE SKIN TO INJURY	27
Part III.—Some Effects of Freezing, of Cooling and of Warming. By THOMAS LEWIS and W. S. LOVE. (<i>From the Cardiac Department, University College Hospital Medical School.</i>)	
THE ISOMETRIC CONTRACTION OF THE FROG'S VENTRICLE	61
By HAROLD N. SEGALL and G. V. ANREP. (<i>From the Department of Physiology and Biochemistry, University College, London.</i>)	
THE SUPPOSED LENGTHENING OF THE ABSOLUTE REFRACTORY PERIOD OF FROG'S VENTRICULAR MUSCLE BY VERATRINE	77
By A. N. DRURY and W. S. LOVE. (<i>From the Cardiac Department, University College Hospital Medical School.</i>)	
THE EFFECT OF QUINIDINE AND STROPHANTHIN UPON THE REFRACTORY PERIOD OF THE TORTOISE VENTRICLE	87
By W. S. LOVE, JR. (<i>From the Cardiac Department, University College Hospital, London.</i>)	
REVISED VIEWS OF THE REFRACTORY PERIOD, IN RELATION TO DRUGS REPUTED TO PROLONG IT, AND IN RELATION TO CIRCUS MOVEMENT	95
By T. LEWIS and A. N. DRURY. (<i>From the Cardiac Department, University College Hospital Medical School.</i>)	
THE GRAPHIC REGISTRATION OF VENOUS PRESSURE IN MAN, ILLUSTRATED BY SOME OBSERVATIONS ON REACTIVE HYPERÆMIA	101
By A. KENDREW. (<i>Cardiac Department, University College Hospital Medical School.</i>)	
THE RELATION OF PULSE FORM TO SOUND PRODUCTION IN ARTERIES...	109
Part I.—The Form of the Sphygmogram During Decompression. By J. CRIGHTON BRAMWELL and SYLVIA K. HICKSON. (<i>From the Cardiographic Laboratory of the Manchester Royal Infirmary.</i>)	